Draw Pharmacology *in your mind*

Angina

If you are a pharmacy student
If you are postgraduate and want to revise pharmacology by an easy way
If you are using any pharmacology reference
this file will aid you
> And wait for more <

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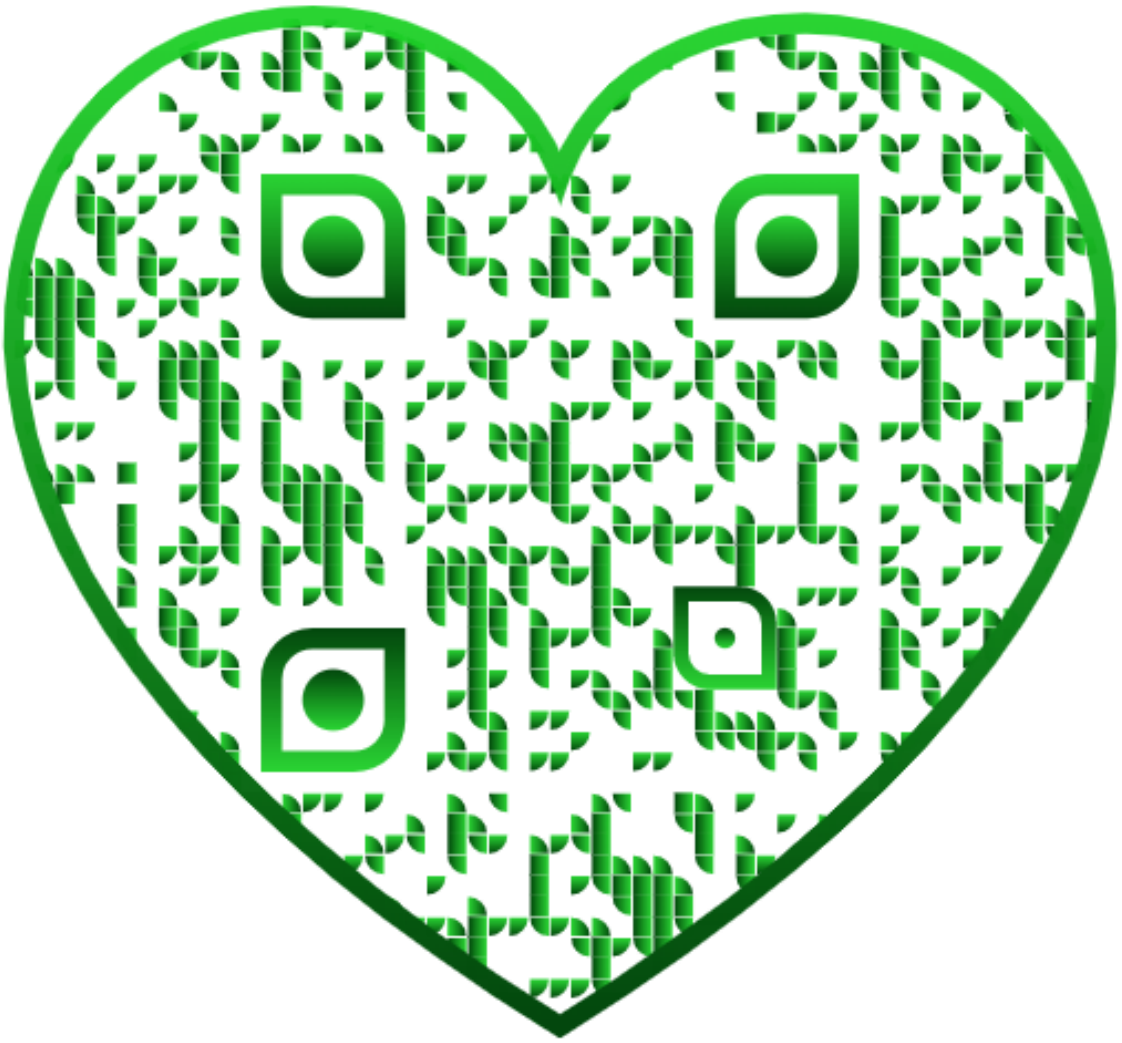
لا تنسونى من صالح دعائكم

Pharmacist. **Alaa Nasr**

د. آلاء نصر



Anti-anginal agents

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Angina

- **Angina** is a Greek verb "to choke" which means → pain or discomfort
- **Heart** is a muscular pump, *an organ like any other organ in the body*, **needs blood to work** properly → this blood reaches the heart through **Coronary arteries** → *you should knowthat* this blood is different from the blood entering the heart to be pumped

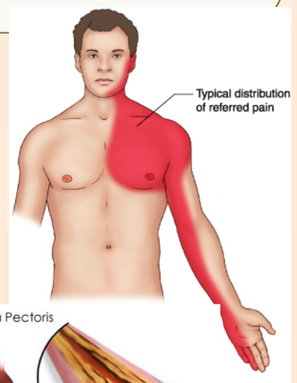
Causes

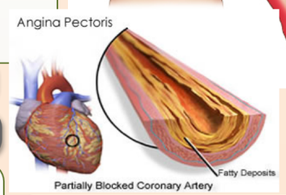
1. Severe **exercise** or physical exertion
2. Psychological conditions → such as emotional **stress**
3. Heavy meals and **obesity**
4. **Atherosclerotic occlusion** → *Degenerative changes in the coronaries due to lipid deposition in the inner walls of the arteries → so, they lose their elasticity and ability to dilate → the lumen becomes narrow!*
5. Getting **cold** (⇓ *temperature*) → *in this case the heart should work more and more to compensate the loss of temperature in the body*

- So, all this cases can cause angina → as work demands of the heart > its blood flow

Symptoms

1. Pain of Sternum عظمة القص referring يسمّع to the left arm and shoulder (or may be both left and right)
2. Breathlessness عدم القدرة على التنفس and suffocating sensation إحساس بالإختناق
3. Anxiety توتر و قلق و الإحساس بإقتراب الأجل





Types

1. Angina pectoris

It happens due to atherosclerotic occlusion = **atherosclerosis**

2. Variant angina

- Due to **coronary spasm** → contraction of smooth muscles of coronary artery → ⇓ blood flow
- **Comes at REST !**

3. Vincent angina !

- It is **NOT in CVS !**
- Spirochaetal infection of mouth and throat

Treatment goals

1. ⇑ **blood flow** in the coronaries
2. ⇓ **O_2 demand** → ⇓ **heart work** → ⇓ energy demand of the heart

1. Nitrites / Nitrates

Mechanism

- **This reduction is done by:**
1. Glutathione organic nitrate reductase enzyme **in the liver**
2. SH group in the nitrate **receptor** (having a reducing capacity)
3. The **bacterial** reduction in the intestinal tract → that may produce nitrites in amount sufficient to cause **Methemoglobinaemia**

- Administered in **organic combination** (ex. Amyl nitrite)
- The term **Nitrites = Nitrates & Nitrites** → As, Nitrates NO_3^- → are **reduced** in the body to NO_2^- → then **NO**

1. Reduction of Nitrates to Nitrites then **NO (Nitric Oxide)**
2. NO activates **"Guanylate cyclase"** enzyme which is responsible for converting **GTP → cGMP**
3. cGMP concentration ⇑⇑ intracellularly
4. cGMP activate certain type of **Protein kinase** enzyme → leading to **dephosphorylation of myosin** *(Note that .. for contraction, actin and myosin should be in phosphorylated form)*

→ So, **binding** between actin and myosin will ⇓ → **contraction** ⇓ → leading to **relaxation** of most of smooth muscles in the body (*GIT, Ureter, Uterus, Bronchi, Biliary duct,* **Blood vessels → vasodilatation**)

- **So, Cardiovascular actions:**
1. **Vasodilatation** of veins & venules *(more sensitive to the dilator effect of Nitrites)*
2. **Relaxation** of capilaries' sphincters
3. **Venous return** *(amount of blood returning to the heart)* **will** ⇓ → so, **Preload** on the heart **will** ⇓

- **But also amount of blood pumped by the heart will** ⇓ *(stroke volume and cardiac output* ⇓*)* → so, **blood pressure will** ⇓ This leads to → **reflex mechanisms mediated by sympathetic nervous system:**

1) Reflex tachycardia
2) Reflex vasoconstriction of some blood vessels → ⇑ peripheral resistance

So, if sympathetic responses are impaired just like in case of taking α-blocker → no compensatory mechanisms → blood pressure ⇓⇓⇓ → blood will be accumulated in abdomen and lower limbs → blood will be very ⇓⇓⇓ in brain → this is called **Nitrite syncope** = Fainting + Nausea + Cold sweat + Shivering

Evidence on Nitrite syncope

1. After administration of Nitrites as **"Crushed pills"** to be inhaled → they produce generalized vasodilatation begins with *immediate and intense flushing in face and neck after administration*
2. **Workers** in factories of explosive substances, *they use nitrates*, so they suffer from:

a) **Headache** → due to vasodilatation of intracranial blood vessels
b) Increased intraocular pressure (IOP) → due to vasodilatation of retinal and other intraocular blood vessels → **Glaucoma**

Side effects

1. Headache
2. GIT upset
3. Flushing
4. Sever hypotension *(in high doses)*
5. Methemogobinaemia *(in infants excess NO_2^- can convert Hemoglobin to Methemoglobin which has low oxygen carrying capacity)*

Members

1. Amyl nitrite & Octyl nitrite

By inhalation (Pearls)

- Short acting → 30 seconds
- Short duration of action → 5 min
- Used for short anginal attacks
- Prophylactic before exercise, stress ..etc

2. Nitroglycerin (Glyceryl trinitrate) (Angised®)

- IV (for emergency)
- Sublingual tablets
- Chewable tablets

*Absorption is from **buccal** cavity*

- Oral tablets (for prophylaxis)
- Ointments
- Patches - implants - Discs *(very slow absorption - can be used for Raynaud's syndrome)*

- Slower onset of action
- Longer duration of action

3. Isosorbide mononitrate
4. Isosorbide dinitrate
5. Isosorbitol dinitrate
6. Erythrityl tetranitrate
7. Mannitol hexanitrate

- **Note that ..** There will be **reflex tachycardia** that minimally ⇑ heart work and that may **oppose** the useful effect of ⇓ cardiac output and the slight hypotension

Anti-anginal effect of Nitrites

Lets take it step by step

- **You may think that** "it is very simple, Nitrites cause vasodilatation of coronaries so, ⇑ blood supply to the heart", but it is more complicated
- What about atherosclerosis in coronaries ? Degenerative changes occur in vessels → ⇓ their ability to dilate ! so, Nitrites can not make further dilatation to coronaries in this case

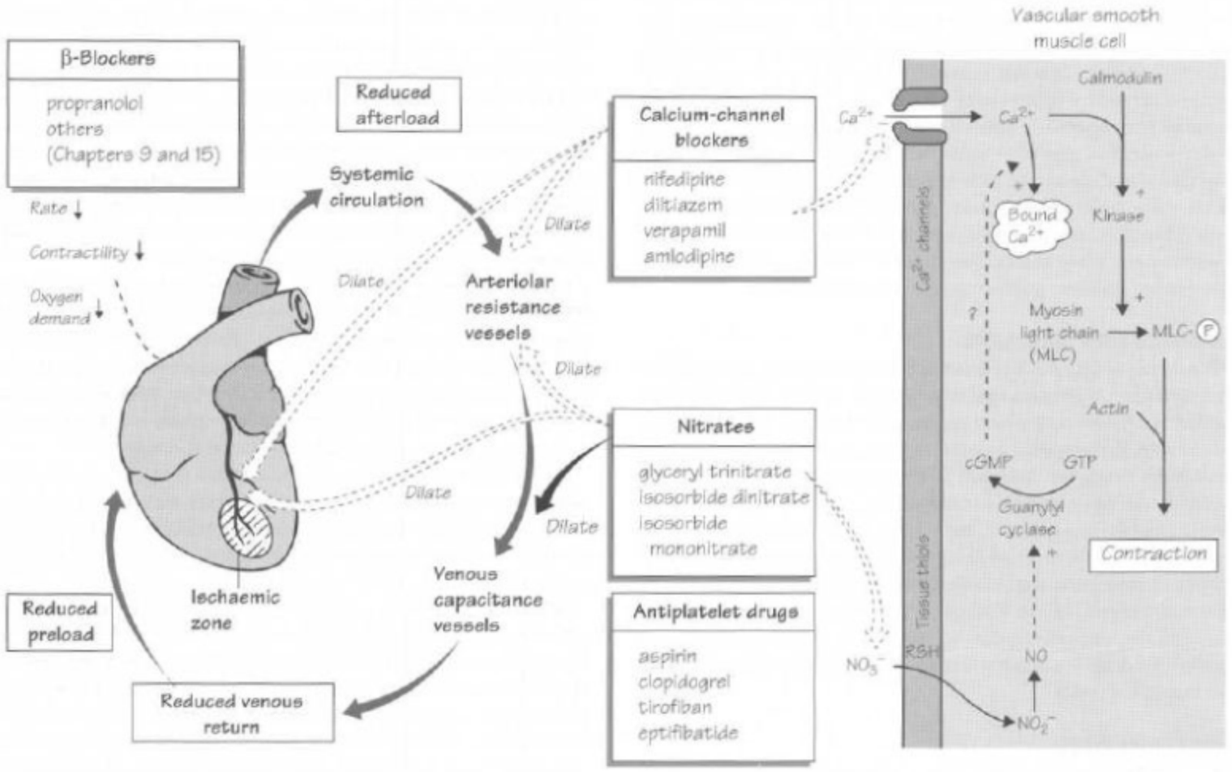
How Nitrites affect angina in this case ?

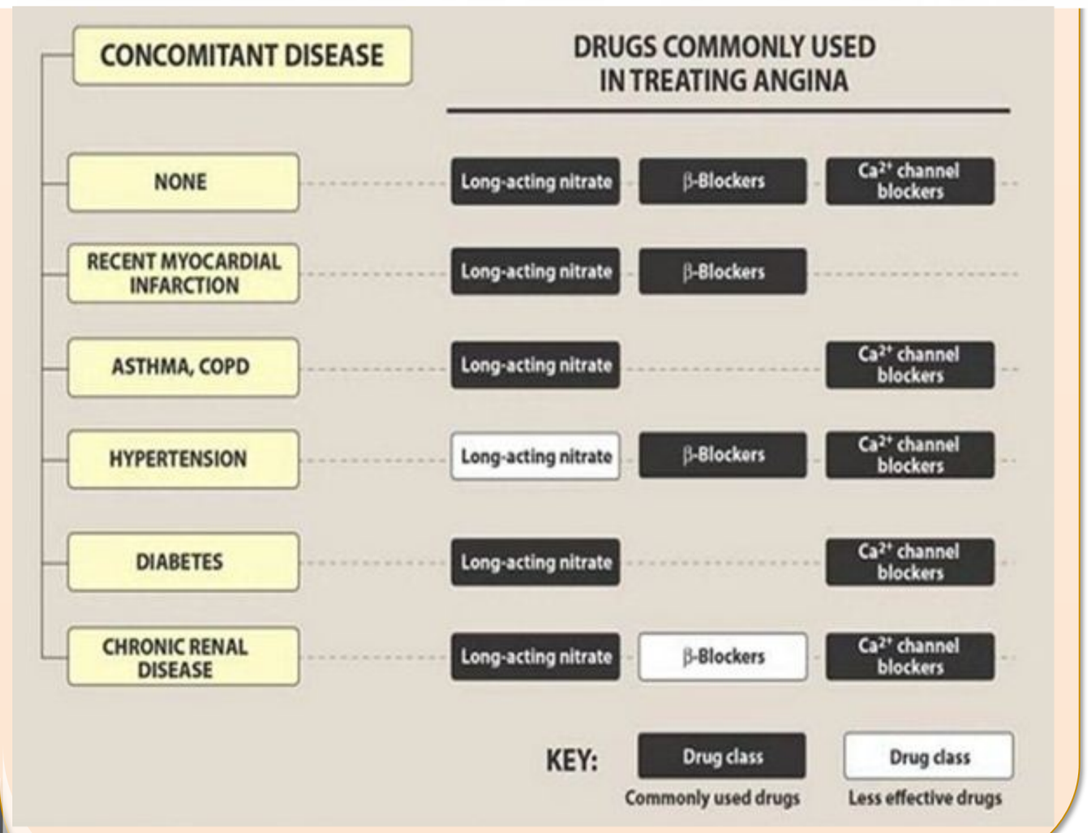
1. They cause **generalized vasodilatation** → so, venous return will ⇓ and also cardiac output will ⇓ → *so, work done by heart and O_2 demand will* ⇓
2. They cause **slight hypotension**, and we know that pumping the blood in dilated blood vessels is easier than pumping in constricted blood vessels → *so, work done by heart and O_2 demand will* ⇓

So, heart preload and heart afterload will ⇓

3. **Mechanical effect** → as venous return ⇓ → ventricles will dilate to a lesser extent → so tension / pressure of ventricular walls on coronaries ⇓ → so, lumen of coronaries will be wider allowing more blood to flow → **so, blood flow to the heart** ⇑

- **Note that ..** Nitrites can treat **variant angina** by dilating the coronaries as there is no atherosclerosis but coronary spasm





- ⇓ **the sympathetic supply** to the heart so,
- Contractility ⇓ → heart work ⇓
- Myocardial energy and **O_2 demand** ⇓
- **But** they cause **vasoconstriction** that may slightly **oppose** the useful effects
- **No effect on blood flow**

Mechanism

- **2nd line** treatment after Nitrites that widely applied for angina
- **ex. Propranolol** *(that has 2 disadvantages look back in "Cardiac arrhythmias" lecture)*

2. β-blockers

Concerning heart
- Heart rate ⇓
- Force of contraction ⇓
- **So, heart work** ⇓

Concerning blood vessels
- Contraction of smooth muscles ⇓ → vasodilatation
- **So, blood flow** ⇑

They block Ca^{+2} entry → so, ⇓ binding between actin & myosin

Mechanism

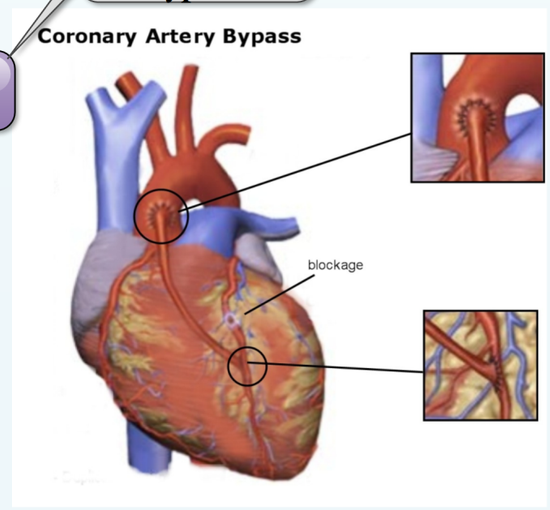
ex. Verapamil - Nifedipine - Amlodipine - Nicardipine - Diltiazem - Cinnarazine
(Pictures of drugs are included in "Cardiac arrhythmias" lecture)

Drug combinations
- Nitrates + β-blocker
- Nitrates + CCBs
- β-blocker + CCBs
- Nitrates + β-blocker + CCBs

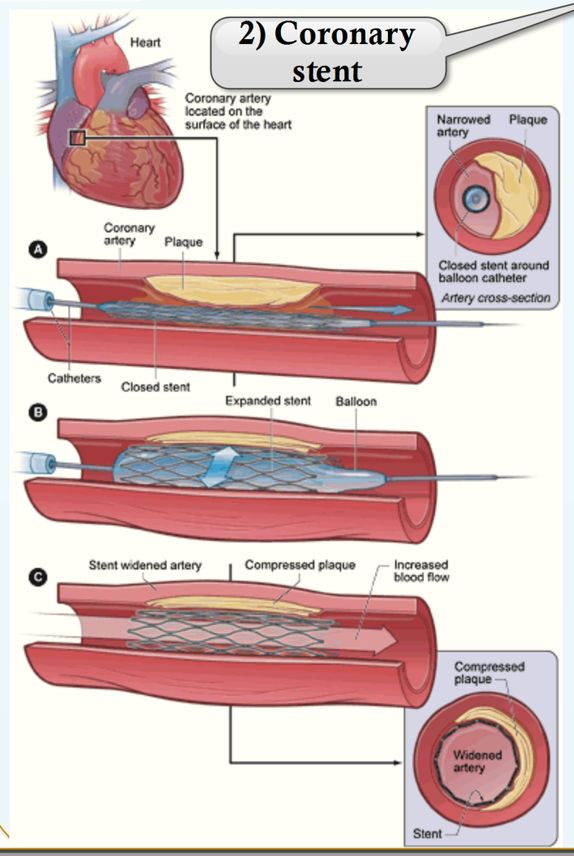
3. Calcium channel blockers (CCBs)

Anti-anginal agents

1) Coronary bypass



2) Coronary stent



4. Surgical procedures

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5. General measures

1. ⇓ **Obesity** and avoiding **heavy meals**
2. ⇓ Plasma levels of **cholesterol and triglycerides** → hyperlipoproteinemia
→ <u>can be reduced by:</u>
a) Avoiding consumption of **animal fat**
b) Using **antihyperlipidemic** drug such as: Cholestyramine - Statins - Finofibrate
3. Avoiding situations of severe **stress**
4. Avoiding **smoking** and **alcohol**